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Consensus

Post-surgical management of non-functioning pituitary adenoma☆

Prise en charge des adénomes hypophysaires non fonctionnels après la chirurgie

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Abstract

Post-surgical surveillance of non-functioning pituitary adenoma (NFPA) is based on magnetic resonance imaging (MRI) at 3 or 6 months then 1 year. When there is no adenomatous residue, annual surveillance is recommended for 5 years and then at 7, 10 and 15 years. In case of residue or doubtful MRI, prolonged annual surveillance monitors any progression. Reintervention is indicated if complete residue resection is feasible, or for symptomatic optic pathway compression, to create a safety margin between the tumor and the optic pathways ahead of complementary radiation therapy (RT), or in case of post-RT progression. In case of residue, unless the tumor displays elevated growth potential, it is usually recommended to postpone RT until progression is manifest, as efficacy is comparable whether treatment is immediate or postponed. The efficacy of the various RT techniques in terms of tumor volume control is likewise comparable. RT-induced hypopituitarism is frequent, whatever the technique. The choice thus depends basically on residue characteristics: size, delineation, and proximity to neighboring radiation-sensitive structures. Reduced rates of vascular complications and secondary brain tumor can be hoped for with one-dose or hypofractionated stereotactic RT, but there has been insufficient follow-up to provide evidence. Somatostatin analogs and dopaminergic agonists have yet to demonstrate sufficient efficacy. Temozolomide is an option in aggressive NFPA resistant to surgery and RT.

Keywords: Non-functioning pituitary adenoma; Gonadotroph adenoma; Silent pituitary adenoma; Non-secreting pituitary adenoma; Pituitary surgery; Radiation therapy

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☆ Consensus of the French Endocrine Society: non-functioning pituitary adenoma.

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Résumé

Après chirurgie, la surveillance des adénomes hypophysaires non fonctionnels (AHNF) repose sur l'imagerie par résonance magnétique (IRM) réalisée 3, voire 6 mois, puis un an après l'intervention chirurgicale. En l'absence de reliquat adénomateux, une surveillance annuelle est recommandée pendant 5 ans, puis 7, 10 et 15 ans après la chirurgie. En cas de reliquat ou d'image douteuse, une surveillance annuelle prolongée précisera l'évolutivité éventuelle de la lésion. Une seconde intervention chirurgicale est justifiée en cas de possibilité d'exérèse complète d'un reliquat, de compression symptomatique des voies optiques, afin de garder une distance de sécurité entre la tumeur et les voies optiques avant irradiation complémentaire ou en cas de progression tumorale après radiothérapie. En présence d'un reliquat, il est le plus souvent justifié (sauf si la tumeur manifeste un potentiel de croissance élevé) de différer la radiothérapie au moment où ce reliquat évolue, son efficacité étant comparable que le traitement soit réalisé d'emblée ou différé. L'efficacité des différentes techniques de radiothérapie sur le contrôle du volume tumoral est comparable. L'hypopituitarisme radio-induit est fréquent, quelle que soit la technique utilisée. Le choix dépendra donc essentiellement des caractéristiques du reliquat (taille, limites, proximité des structures radio-sensibles avoisinantes). Avec les radiothérapies stéréotaxiques en dose unique ou hypofractionnées, on espère une fréquence moindre des complications vasculaires et des rares tumeurs cérébrales secondaires ; mais le recul reste insuffisant. Les analogues de la somatostatine et les agonistes dopaminergiques n'ont pas fait la preuve jusqu'alors d'une efficacité suffisante. Le témozolamide peut être discuté chez les patients présentant des AHNF agressifs après chirurgie et radiothérapie.

Mots clés : Adénomes hypophysaires non fonctionnels ; Adénomes gonadotropes ; Adénomes hypophysaires silencieux ; Adénomes hypophysaires non sécrétants ; Chirurgie hypophysaire ; Radiothérapie

Despite recent progress in neurosurgery, surgical treatment of non-functioning pituitary macroadenoma (NFPA) often achieves only partial tumor resection and recurrence is frequent without adjuvant therapy [1–11] (Table 1).

1. Factors for recurrence of non-functioning adenoma

Several studies have focused on factors for recurrence in NFPA, but were often retrospective, with small series and variable lengths and methods of follow-up. Criteria for recurrence were variable, sometimes failing to make the distinction between progression of postoperative residual tumor and true recurrence: i.e., new tumor onset after complete resection. However, there have been several recent meta-analyses [12,13] reporting higher recurrence rates in NFPA than in secreting adenoma. This has varied little over the last 30 years [14,15].

1.1. Clinical factors

The best identified recurrence factor is postoperative adenomatous residue (Table 1). In apparently complete resection (postoperative MRI interpreted as being normal), the recurrence risk is around 10–20% at 5 years and 30% at 10 years [2,5,8,10,16–18]. In case of postoperative tumoral residue, recurrence risk ranges from 25 to 40% at 5 years and exceeds 50% at 10 years, according to recent findings [2,5,7–11,16–18]. Chen et al. [12], in a meta-analysis of 19 studies of acceptable quality (modern imaging, long follow-up), reported that the recurrence rate in patients without identifiable residue ($n = 371$) was 12%, with 96% remission at 5 years and 82% at 10 years; in case of postoperative adenomatous residue ($n = 600$), the recurrence rate was 46%, with 56% progression-free survival at 5 years and 40% at 10 years. Mean doubling time for adenomatous residue was 3.4 years.

Young age, gender and initial tumor size are non-systematic recurrence factors [4,11,19,20]. Apoplexy is not a guarantee of definitive remission. Recurrence risk is increased in invasive tumor with extra-sellar progression (cavernous sinus, clivus), but this is also a risk factor for incomplete resection [4,10,21].

1.2. Histologic factors

Progression may be bound to histologic type. Prognosis is classically poorer in silent corticotroph adenoma (SCA: 4–10% of NFPAs). In Yamada et al.'s study [22], the cavernous sinus was invaded in 85% of SCAs, compared to only 38% of non-immunoreactive adenomas and 11% of gonadotroph adenomas. Recurrence rates in SCA are comparable to those in other NFPAs, but recurrence, when it occurs, is earlier and more aggressive [23–26]. Prognosis in silent mixed GH-PRL adenoma is likewise poorer [10].

As in other types of pituitary adenoma, tumor biomarker expression could contribute to determining prognosis [27–29]. Results regarding predictive value, however, have been contradictory [15,19–21,30]. Several reports found no correlation between Ki67 and/or p53 expression and recurrence risk at 10 years [15,20]. The relation between Ki67 expression and invasion is, moreover, variable [15]. However, in a recent study by Ramirez et al., analyzing the expression of Ki67, PTTG, FGFR4 and SST2 and 5 in 74 gonadotroph and non-immunoreactive adenomas, Ki67 (mean, 1.49) was the only biomarker with expression linked to tumor behavior [30]: on multivariate analysis, expression correlated with tumor diameter (>3 cm) and risk of tumor recurrence (odds ratio: 1.4). Likewise Righi et al., studying 75 NFPAs with a mean 6 years' follow-up, found >3% Ki67 expression in 5% of tumors without recurrence versus 30% in those with, while mitosis index and p53 expression were similar. Ki67 predicted recurrence with high specificity

Table 1
Results of surgery in NFPA and recurrence risk according to postoperative tumor residue.

Authors	Refs	Total/without RT	FU (years)	Type of study	Recurrence in absence of residue	Recurrence in case of residue
Turner et al. (1999)	[1]	65/65	6.3	Retrospective	9/31 (20%)	12/34 (35%)
Woollons et al. (2000)	[2]	72/22	5.3	Retrospective	2/11 (18%)	8/11 (73%)
Soto-Ares et al. (2002)	[3]	51/51	5.6	Prospective	0/17 (0%)	13/34 (38%)
Greenman et al. (2003)	[4]	122/108	4.2	Prospective	6/30 (20%)	41/78 (53%)
Ferrante et al. (2006)	[5]	226/150	8.1	Retrospective	14/73 (19%)	45/77 (58%)
Dekkers et al. (2006)	[6]	97/91	6	Retrospective	1/27 (4%)	9/64 (14%)
van den Bergh et al. (2007)	[7]	122/46	8	Retrospective	1/18 (6%)	16/28 (57%)
Losa et al. (2008)	[8]	436/355	4.5	Prospective	PFS 5 years: 87.1%	PFS 5 years: 39.2%
O'Sullivan et al. (2009)	[9]	126/126	5.7	Retrospective	0/26 (0%)	53/100 (53%)
Brochier et al. (2010)	[10]	142/127	6.9	Retrospective	10/42 (24%)	46/85 (54%)
Reddy et al. (2011)	[11]	144/144	6.1	Retrospective	2/29 (7%)	49/115 (43%)
Total		1603/1285			45/304 (15%)	292/626 (47%)

PFS: progression-free survival.

(89%) but poor sensitivity (54%), which suggests that new thresholds need to be identified in these adenomas [21]. Finally, several recent studies related Ki67 expression to tumor doubling time [19,31,32]. These findings suggest that Ki67 is not predictive of recurrence risk but could be an effective index of progression risk in postoperative adenomatous residue. A new adenoma classification includes markers for radiologic and/or histologic invasiveness, and for proliferation (Ki67, p53, mitosis index: proliferation corresponding to 2 of the 3 being abnormal), improving the identification of residues liable to progress over the long-term [29].

Other markers are under assessment. PTTG expression is constant and non-discriminative [30]. Expression of subtype 2 and 5 somatostatin receptors is lower in recurrent adenoma [33]. Cyclin D1 is a proto-oncogene implicated in oncogenesis and pituitary invasion; recent studies, however, suggest its expression is not practically contributive to prognosis [34,35]. Finally, other studies focused on the expression of angiogenesis markers, notably VEGF and FGFR4 receptors [30,36]. It was very recently shown that endocan, a proteoglycan secreted by endothelial cells, is expressed in pituitary adenoma: in a series of 107 cases at 8 years' follow-up, expression was significantly associated with mitosis index, tumor size and risk of progression [37]. The focus now is on identifying molecular prognostic markers (ENC1, CLDN9, etc.), not yet available in clinical practice [38–41].

2. Postoperative follow-up of NFPA

2.1. Imaging

Post-surgical radiologic monitoring is essential in NFPA, due to the frequent lack of clinical symptoms accompanying progression. Follow-up is preferably on MRI, pituitary CT scan being reserved to cases where MRI is contraindicated. Good reproducibility is essential to the quality of follow-up, and can ideally be achieved by volume acquisition with 3D reconstruction; failing this, successive acquisitions should be made under identical technical conditions, in the same reference plane (e.g., coronal slices perpendicular to the subcallosal plane). It is important, for interpretation, to provide the radiologist with the preoperative MRI scan and operative report, and a reference MRI scan taken 3 to 6 months after surgery. The imaging protocol comprises thin (2–3 mm) sagittal T1, coronal T1 before and after gadolinium injection, coronal T2, or axial T1-weighted slices.

Immediate postoperative MRI is not systematic, but may be prescribed for suspected postoperative complications or possible early surgical revision in the days following primary surgery [42]. Otherwise, the first MRI will be performed at 3 or 6 months [3,43]. A 6-month interval reduces the rate of postoperative remodeling artifacting interpretation, but a 3-month interval is to be preferred in case of signs of large residue potentially threatening the optic pathways. Repeat MRI at 1 year is systematic. These two MRI scans serve as references for subsequent follow-up [3,43].

Precise interpretation of the postoperative reference MRI is essential, to determine whether residue, and hence a risk of progression, is present. When detectable adenomatous residue is absent or doubtful, MRI is repeated annually for 5 years and then at 7, 10 and 15 years. Systematic radiological follow-up can then be stopped if there are no clinical signs, recurrence or suspect images. Adenomatous residue is associated with recurrence, usually within 1–5 years [14] but sometimes later, more than 10 years after primary surgery (20% of recurrences according to Reddy et al. [11]). In case of adenomatous residue or suspect image, MRI is repeated annually for 5 years and then every 2–3 years in absence of progression, the schedule being adjusted on a case-by-case basis according to tumor size, distance from the optic pathways or doubt as to progression. Long intervals between check-ups entail a risk of loss to follow-up, requiring particular vigilance (Fig. 1).

At each check-up, the new MRI should be compared against the postoperative reference [6,15,42,44]: progressive residue increase could be overlooked if the new MRI were to be compared only with the previous one, since adenoma growth is often slow.

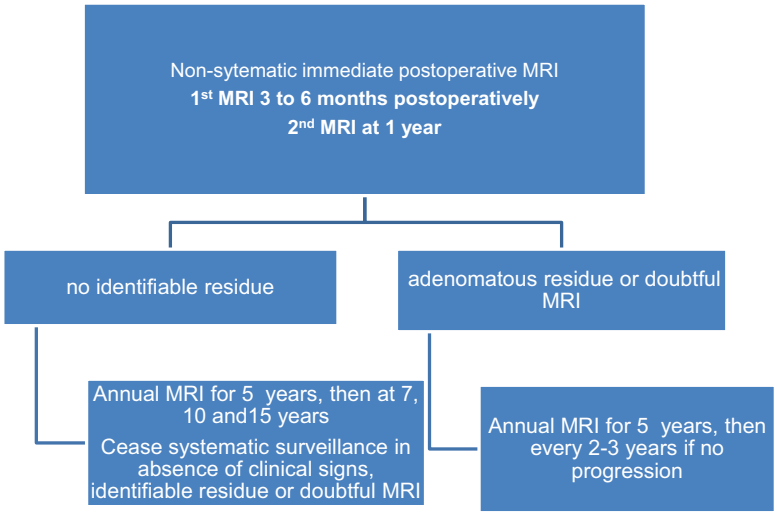

Fig. 1. MRI surveillance after surgery for non-functioning pituitary adenoma.

2.2. Ophthalmologic follow-up

In case of preoperative ophthalmologic abnormality, a check-up is made 3 months after surgery, exploring visual acuity, visual field, fundus and possible diplopia. The examination is repeated every 6 months until maximum improvement is achieved, especially when initially severe visual disorder contraindicated driving; such contraindications are to be regularly reassessed over follow-up. Surveillance may then be less frequent. In the absence of any visual impairment on the first postoperative examination, follow-up can be stopped if there is no suprasellar residue close to the optic pathways. If radiation therapy (RT) is performed, prolonged annual follow-up is necessary, especially after a hypofractionated or single-dose regime, to screen for RT-related complications that may show onset several years post-therapy.

2.3. Biologic follow-up

Biological hormonal assessment, performed 3 months postoperatively, estimates recovery of hypopituitarism diagnosed preoperatively and the definitive nature of post-surgical hypopituitarism. Hormonal exploration is repeated to adapt replacement therapy if necessary in case of functional alarm signs or increased volume of any residual tumor. Such deficits are frequent after RT, requiring twice-yearly pituitary hormone assessment, as described above in the review by Raverot et al.

3. What treatment can be offered for residue or recurrence?

3.1. Surgical revision

Between 30 and 48% of NFPAs undergo surgical revision on a trans-sphenoid approach [8,9], either early for large residue, or later during tumoral progression.

Revision surgery does not seem to enhance tumor control, with persistent residue in 72% of cases. Benefit is less than with RT. Efficacy in terms of visual recovery also seems to be less than for primary surgery (58% versus 90%). Moreover, surgical complications are slightly more frequent [45].

Indications for revision surgery for recurrence of NFPA should take account of the primary surgery report and of residue size and location. Surgery is indicated for progressive residue accessible for complete resection, which can be limited by invasion of one or both cavernous sinuses; in case of persistent or recurrent symptomatic optic pathway compression; to obtain anatomic conditions allowing stereotactic RT (3–5 mm) safety margins between adenoma and optic pathways; or in case of post-RT tumor progression. Primary surgery may also be planned in 2 steps: intrasellar resection, with a second step after descent of the suprasellar contingent.

Remodeling of classical anatomic landmarks (sphenoidal rostrum, sphenoid sinus septum) and impaired discrimination between different intrasellar tissues may hinder surgery. Some authors recommend intraoperative neuronavigation in such cases, but this remains a matter of debate.

3.2. Radiation therapy

After postoperative RT, recurrence risk in NFPA is considerably reduced, 10-year progression-free survival being greater than 90% in most series [7,10,12,45–50] (Table 2). A recent meta-analysis [13] reported a relative risk of recurrence of 1.97 without versus with RT.

It is thus unsurprising that postoperative RT has been recommended as a complement to surgery for several decades, although controversy remains as to indications and timing, due to associated complications. Controversy persists mainly because of the lack of randomized prospective efficacy studies for postoperative RT in NFPA. Most studies have been retrospective and observational, and systematic analysis is hindered by numerous selection biases and study characteristics: varying definitions of

Table 2
Efficacy of fractionated conformal RT on progression/recurrence risk in NFPA.

Authors	Refs	Number of patients	FU (years)	With/without RT	% recurrence-free at 5 years		% recurrence-free at 10 years	
					With RT	Without RT	With RT	Without RT
Jaffrain-Rea et al. (1993)	[46]	57	7.1	24/33	100%	70%	96%	55%
Gittoes et al. (1998)	[48]	126	9	81/355	93%	68%	93%	47%
Woollons et al. (2000)	[2]	72	5.3	50/22	72%	34%	–	–
Park et al. (2004)	[49]	176	4.3	44/132	98%	85%	98%	50%
van den Bergh et al. (2007)	[7]	122	8	76/46	95%	49%	95%	22%
Olsson et al. (2009)	[50]	235	10	62/173	–	–	94%	62%
Brochier et al. (2010)	[10]	142	6.9	15/127	100%	70%	91%	52%

recurrence, varying rates of patients free of visible residue following surgery, varying length of follow-up (often insufficient), and preferential selection of patients at high risk of recurrence in RT groups. In a very few studies, RT was systematic after NFPA surgery, but most centers reserve RT to more aggressive tumors, large supra- or extra-sellar residual tumor or confirmed recurrence. Such biases systematically tend to weigh against RT in efficacy studies.

3.2.1. Types of radiation therapy

The first types of RT (known as "classical" or "conventional") used a small number of beams, with 2D dosage study and relatively wide (and often poorly delineated) margins. High total and fractional radiation doses led to relatively high rates of severe complications such as cerebral necrosis and ophthalmologic lesion. Later, particle accelerators delivering high-energy X photons instead of cobalt improved depth rendering and reduced the radiation field penumbra. Increasing the number of beams, with total doses of 45–50 Gy and fractionated doses of 1.8–2 Gy and the introduction of simulators to locate target volumes according to imaging data, with direct linkage to dose calculation, brought further considerable improvements. The "conformal" technique uses 3D target location and dosimetry, and multi-slice fan-beam collimators improve targeting of complex volumes. Finally, increasing the number of non-coplanar beams and being able to modulate intensity further reduce irradiation of healthy neighboring tissue.

Radiosurgery is 1-step RT. The objective is to superimpose target limits and the chosen reference isodose, so that the dose diminishes rapidly beyond the target, optimizing sparing of healthy adjacent structures. This requires an invasive stereotactic frame, to achieve precise positioning within 1 mm, a high-resolution imaging system, and 3D dosimetry. The devices used are the Gamma-Knife (201 cobalt^{60} sources on a hemisphere) and the linear accelerator (LINAC). The marginal dose is usually 13–16 Gy in NFPA. This type of RT is feasible only if the target volume is clearly visible, small (<2–3 cm on the long axis) and sufficiently remote from the optic pathways to ensure <8 Gy irradiation of the chiasm and optic nerves.

Fractionated stereotactic RT associates the ballistic precision and multiple beam entries of radiosurgery to the principle of healthy tissue radioprotection by fractioning. The total dose is 45–50 Gy by 1.8–2 Gy fractions.

CyberKnife is a miniaturized accelerator with a robotic arm, enabling hypofractionated stereotactic RT (3–9 sessions, depending on the team) with a non-invasive contention system based on the technical and dosimetric principles of radiosurgery.

Proton therapy is not widely available and thus little used for NFPA.

3.2.2. Results of radiation therapy

3.2.2.1. Fractionated conformal radiation therapy. Many studies now have demonstrated the efficacy of fractionated RT in preventing postoperative recurrence of NFPA (Table 2). For simplicity's sake, Table 2 presents only the more recent publications (1991–2010), analyzing recurrence risk with sufficient follow-up, and including both patients receiving postoperative RT and those managed by surgery alone.

It emerges that almost all the reports show highly significant benefit of RT for non-recurrence rates at 5 years (without RT, 66 ± 19%; with RT, 94 ± 9%) and 10 years (without RT, 52 ± 16%; with RT, 92 ± 6%). Global relapse fell about 3-fold: 321/986 without RT (32%) versus 55/468 with (12%).

Two factors bear on the benefit of RT: length of follow-up, accentuating the difference in recurrence even after 10 years; and postoperative residual tumor, in presence of which RT shows even clearer benefit, with mean global relapse falling from 62 to 17% [2,5,10]. Other factors may also influence efficacy, such as tumor type (oncocytic tumor being the most radioresistant [51]) or irradiation field area [52], but these findings have not been formally validated.

Late RT seems to be as effective in tumor control as immediate postoperative RT [49].

3.2.2.2. Fractionated stereotactic radiation therapy. Efficacy studies of fractionated stereotactic radiation therapy report a smaller number of patients, with mean follow-up usually not exceeding 5 years [53–57] (Table 3). Results are generally similar to those of classic RT, with tumoral control achieved in more than 95% of cases at 5 years.

3.2.2.3. Radiosurgery. Radiosurgery is usually postoperative, reserved for small, well-defined residues remote from the optic pathways (Table 4).

Most studies involved smaller numbers of patients, with 2.5–6.5 years' follow-up [58–68]. Results were generally

Table 3
Efficacy of fractionated stereotactic RT on recurrence risk in NFPA.

Authors	Refs	Number of patients	Recurrence (%)	Median FU (years)	5-year RFS %
Milker-Zabel et al. (2001)	[53]	68[a]	5	3.2	93
Paek et al. (2005)	[54]	65	2	2.5	98
Colin et al. (2005)	[55]	110[a]	1	4	99
Minniti et al. (2006)	[56]	91[a]	3	2.8	98
Schalin-Jäntti et al. (2010)	[57]	20	0	4.5	100

RFS: recurrence-free survival.
[a] Studies including functioning tumors.

similar to those of classic RT, with tumoral control achieved in 90–100% of cases at 5 years. Data for 512 patients managed in 9 North American centers showed 95 and 85% tumoral control at 5 and 10 years, respectively [69]. Efficacy was comparable to that of first-line treatment [70]. A recent meta-analysis found better tumoral control in tumor volumes less than 4 ml [71]. There are no controlled studies comparing radiosurgery versus surgery alone.

3.2.2.4. CyberKnife radiotherapy. Tumoral control was achieved in 98% of cases in 100 patients at a mean 33 months (range: 18–118.5 months) after CyberKnife RT for NFPA residue with or without progression [72].

Wilson et al. [68], in a recent study, compared results in conventional fractionated RT, LINAC stereotactic radiosurgery and fractionated stereotactic RT. Allowing for various inclusion biases (historic series for conventional fractionated RT, smaller tumors remote from the optic pathways for stereotactic radiosurgery, etc.) they concluded that efficacy in terms of tumoral control was comparable between these types of RT (Table 4).

3.2.3. Complications of radiation therapy

3.2.3.1. Fractionated conformal radiation therapy. Hypopituitarism is the most frequent complication of fractionated RT (Table 5). Onset may be at several years, progressing over time. It is pituitary and especially hypothalamic deficiency, thus frequently associating moderate hyperprolactinemia. Frequency ranges between 50 and 80% in follow-up exceeding 10 years [45]: prolonged regular follow-up is thus required after RT. Reducing total dose to <50 Gy and dose per fraction to 1.8 Gy, increasing beam number and 3D dosimetry have succeeded in eliminating radionecrosis [73]. Ophthalmologic complications are rare (<1%), and sometimes late [73], associated with baseline optic pathway involvement.

Radiation-induced cerebral tumor after conventional RT for pituitary adenoma is a rare but well-established risk. It may be astrocytoma [45,74], glioma or glioblastoma [47,73], sarcoma [45,74,75] or meningioma [45,74] (observed in some cases 20 years post-RT). In a series of 426 adenomas treated by RT between 1962 and 1994, the risk was 2% at 10 years, 2.4% at 20 years and 8.5% at 30 years [74].

Table 4
Efficacy of radiosurgery on recurrence risk in NFPA.

Authors	Refs	Number of patients	Recurrence (%)	Median FU (years)	5-year RFS %
Wowra and Stummer (2002)	[58]	45	7	4.5	93[a]
Sheehan et al. (2002)	[59]	42	2	2.5	NA
Petrovich et al. (2003)	[60]	56	0	3	100[a]
Iwai et al. (2005)	[61]	31	13		93
Picozzi et al. (2005)	[62]				
With Gamma-Knife		51	ND	5	51
Without Gamma-Knife		68	ND	5	90
Mingione et al. (2006)	[63]	90	8	3.75	NA
Liscák et al. (2007)	[64]	79	0	5	100
Pollock et al. (2008)	[65]	62	3	5.4	95
Höybye and Rähn (2009)	[66]	168	5	3.5	94
Losa et al. (2011)	[67]	23	4	6.5	
Sheehan et al. (2013)	[69]	512	6,6	3	95
Mixed study					
Wilson et al. (2012)	[68]				
RS (LINAC)		51	0	4.2	100
FSRT (LINAC)		67	9	5.1	93
FCRT		53	13	4.4	87

RFS: recurrence-free survival; FSRT: fractionated stereotactic radiation therapy; RS: radiosurgery; LINAC: linear accelerator; FCRT: fractionated conformal radiation therapy.
[a] RFS at 3 years.

Table 5
Efficacy and complications for the different types of RT.

	Conventional/conformal	Fractionated stereotactic	CyberKnife	LINAC	Gamma-Knife
Tumoral control	5 years: 72–100% 10 years: 93–98% 20 years: 70–90%	93–100%	93–98%	93–98%	89.9–100%
Hypopituitarism	↗ with time 50–80% at >10 years	5–35%	0–20%	0–9.8%	7–40%
Ophthalmologic complications	<1%	<1%	0–1%	<2%	0–13.7%
Secondary tumor	1.3–2% at 10 years 1.9–2.7% at 20 years	?	?	?	Rare glioblastoma, sarcoma
Radionecrosis	↘↘↘	↘↘↘	?	Reported	?
Vascular	Conventional: RR 1.5 to 4 (dose, female, surgery)	Not reported	Not reported	Intracavernous carotid stenosis, stroke	Intracavernous carotid stenosis
Other	?	?	?	?	Trigeminal neuralgia

Cognitive disorders, varying from subject to subject, have been reported in patients followed for pituitary adenoma, but with no clear demonstration of the involvement of RT [76] in the absence of any prospective studies. The pathophysiology of cognitive disorders is probably multifactorial: anatomic impact of large adenoma, overlooked or poorly compensated hormone deficits, surgical sequelae, etc. The impact if any of RT on quality of life is controversial [77] and also seems to be multifactorial: age and gender, type of surgery, possible hypopituitarism and treatment.

Ionizing radiation may trigger a reaction cascade in endothelial cells and leukocytes (expression of adhesion molecules, cytokines and chemokines, etc.), leading to a pro-thrombotic state and vascular inflammatory reaction. This post-RT vascular inflammatory state may, in the medium- to long-term, induce or aggravate atherosclerosis [78]. Hypopituitarism, whether or not secondary to RT, may also increase vascular risk [79]. Stewart et al. demonstrated in mouse that RT was an independent factor for lesions to irradiated arteries, with possible synergy with known cardiovascular risk factors [80]. The first human studies were prompted by excess post-RT mortality not accounted for by progression of the adenoma or RT-induced tumor. Vascular risk is elevated in female subjects and in case of pituitary surgery preceding RT [81]. Stroke has also been associated with classical external ("conventional") RT [73,79,81,82]. The specific technique may be implicated, notably the use of two lateral beams, margin width, and use of 2D dosimetry. Vascular lesions have not been reported following fractionated stereotactic RT, but few studies reported such vascular complications precisely [83].

3.2.3.2. Radiosurgery. In the short-term, headache (<5%), nausea, asthenia and pain at the stereotactic frame anchorages have been reported in Gamma-Knife and LINAC radiosurgery.

Following Gamma-Knife radiosurgery, the risk of visual impairment ranges, depending on the series, from 0 to 13.7%. Onset may be very early, within days, but is usually later, with a reported maximum of 93 months. Several risk factors have been identified: history of conventional RT, iterative radiosurgery, pre-existing visual pathway involvement, multiple isocenters [84], large tumor volume [69] and, above all, <3–5 mm distance from the chiasm and >8 Gy [85] (or according to other authors 10 Gy [86]) irradiation planned for the chiasm. RT-induced oculomotor impairment has been reported with Gamma-Knife [84], sometimes being transient. Even so, the cranial nerves passing through the cavernous sinus seem to be more radioresistant than the optic nerve or the chiasm [87]: 19–23 Gy were delivered without clinically serious impact [88,89]. Systematic 6-monthly ophthalmologic monitoring during the first 4 years and then annually for 10 years should be implemented. A rare clinical presentation of ocular neuromyotonia has been reported following Gamma-Knife RT [90].

Following Gamma-Knife RT, onset of hypopituitarism is not always screened for optimally and systematically. Follow-up duration is variable and in many cases too short. For all these reasons, a reliable epidemiology for these complications is difficult to determine. In the literature, the incidence of RT-induced hypopituitarism varies between 7 and 40%. Onset may be very late. Identified risk factors comprise target volume (>4 ml) [71], residue proximity to the pituitary gland and stalk, maximum dose received by the pituitary gland >15 Gy and by the distal infundibulum >17 Gy [69,91–93], no healthy pituitary gland seen on MRI [92], pre-existing partial hypopituitarism [93], and previous RT [69].

Radionecrosis has not been reported following Gamma-Knife RT in NFPA, although there have been some few cases following LINAC radiosurgery (<3%).

Rare cases of trigeminal neuralgia and intracavernous internal carotid thrombosis [94] have been reported with Gamma-Knife and LINAC. There are as yet insufficient data to assess the risk of onset of cognitive disorders. Three cases of RT-induced tumor following Gamma-Knife treatment of a pituitary lesion have been reported [95,96].

3.2.3.3. Hypofractionated stereotactic RT (CyberKnife). Data are as yet very preliminary for CyberKnife, although hypofractionation should significantly reduce side effects. Treatment is well-tolerated ophthalmologically if the chiasm and/or optic

nerves do not receive too much radiation. A single case of transient oculomotor involvement has been reported [97]. Hypopituitarism prevalence has been estimated at 0 to 20%. There have been no reports of radionecrosis or secondary tumor, but follow-up has been short.

3.2.3.3.1. To sum up. The efficacy of postoperative RT in NFPA now seems undeniable, whatever the technique Late RT seems to be as effective in tumor control as immediate postoperative RT. Benefit emerges more clearly with longer follow-up and for larger postoperative residue. Benefit is, however, to be weighed against known side effects, notably RT-induced hypopituitarism and secondary brain tumor. The impact of the various types of RT on cognitive function and quality of life remains very poorly elucidated.

Most experts now agree that immediate postoperative RT is not indicated after complete tumor resection, as the recurrence risk is low. Treatment can be postponed without loss of efficacy, but regular radiological surveillance should be maintained over a period of many years.

In the absence of significant and, especially, invasive tumor residue, indications for RT should take account of risk factors for regrowth, patient age and history, and any hypopituitarism. In most cases, regular surveillance can be the first-line attitude, with treatment postponed until the residue shows progression and/or becomes threatening. RT is indicated if the tumor shows elevated growth potential and the risk of hypopituitarism is not a major problem.

The efficacy of the various types of RT is comparable in terms of tumoral control (Table 5) and the choice depends on the size, limits and location of the residue with respect to neighboring neural structures and on the center's particular experience with the various techniques. Before indicating single-dose RT, the risk/benefit ratio needs to be assessed: there is no point in trying to minimize complications by adopting a low-dose attitude if this would lead to insufficient tumoral control.

3.3. Medical treatment

Gn-RH agonists and antagonists have been proved ineffective for reducing NFPA volume.

The discovery of dopaminergic receptors (especially type D2 [98,99] [100], but also D4) and somatostatin receptors (SST3 and SST2) [30,101] within NFPA, plus in vitro findings, have led to dopaminergic agonists and somatostatin analogs being deployed in NFPA. Series have been small and heterogeneous (inclusion criteria, treatment being administered in first-line or not, systematically after surgery or only in case of recurrence, efficacy assessment criteria, presence of visual signs, comparison against control group, etc.). No long-term prospective studies against placebo have been performed. The dopaminergic agonists (bromocriptine, quinagolide and especially cabergoline), doses (up to 3 mg/day for cabergoline) and treatment durations (1 to 93 months) all varied. It is difficult to assess efficacy in terms of tumor volume in the absence of any controlled studies. Volume reduction has been reported [98,100,102] and seems to be associated with D2 receptor expression (especially the short isoform) within the tumor. Treatment sometimes leads to improvement in ophthalmologic disorders, even if there is no significant reduction in tumoral volume.

The somatostatin analogs and treatment duration (1–37 months) again varied between studies [103]. Volume reduction was reported in a small percentage of cases. Treatment may provide rapid relief of headache and visual field defect, once again possibly independently of an antitumoral action. Somatostatin receptor scintigraphy is non-predictive of analog effects [103,104]. There are no data regarding tumor progression after treatment termination. An association of dopaminergic agonists and somatostatin analogs was tried, without improving efficacy [105]. The interest of pasireotide, a novel somatostatin analog with affinity for all SSTs except subtype 4, was suggested in an in vitro study [106]; in vivo data are presently lacking. In conclusion, none of these medical therapies has shown sufficiently reliable significant efficacy in terms of tumor volume to be recommended in case of failure of surgery in NFPA.

Temozolomide is an oral alkylating agent that is effective in pituitary carcinoma and aggressive adenoma (mainly lactotroph or corticotroph) [107]. Low tumoral expression of O^6-methylguanine DNA methyltransferase (MGMT) is associated with good temozolomide response. A recent study [31] associated lower MGMT expression in recurrent than non-recurrent NFPA, suggesting a possible interest of temozolomide in aggressive NFPA.

Recent reports suggest that Raf/MEK/ERK and PI3K/Akt/mTOR (*mammalian target of rapamycin*) pathway regulation abnormalities are implicated in cell proliferation in pituitary adenoma [108]. The action of rapamycin is down-regulated by Akt phosphorylation, which in turn is reduced by SST2 stimulation. Thus, an in vitro study showed rapamycin sensitization of adenomatous cells by addition of octreotide [109], suggesting a theoretic interest of concomitant somatostatin analog and mTOR pathway inhibitor treatment.

4. Conclusion

Post-surgically, if there is no identifiable adenomatous residue or in case of doubtful image, prolonged regular surveillance should be implemented, as the risk of complications following secondary treatment (surgery or radiotherapy) is greater than that of recurrence and/or complications related to recurrence.

In case of adenomatous residue: morphology (size, limits, distance from optic pathways, cavernous sinus invasion), anatomopathology (immunohistochemistry, Ki67, p53, mitosis index), residue progression, patient age and history and aptitude for regular prolonged surveillance, any hypopituitarism, and the feasibility of and experience with secondary therapies in the center are factors in decision-making, in agreement with the patient, in a multidisciplinary team meeting involving the neuroradiologist, neurosurgeon, radiotherapist and endocrinologist.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

[1] Turner HE, Stratton IM, Byrne JV, Adams CB, Wass JA. Audit of selected patients with nonfunctioning pituitary adenomas treated without irradiation – a follow-up study. Clin Endocrinol (Oxf) 1999;51:281–4.

[2] Woollons AC, Hunn MK, Rajapakse YR, Toomath R, Hamilton DA, Conaglen JV, et al. Non-functioning pituitary adenomas: indications for postoperative radiotherapy. Clin Endocrinol (Oxf) 2000;53:713–7.

[3] Soto-Ares G, Cortet-Rudelli C, Assaker R, Boulinguez A, Dubest C, Dewailly D, et al. MRI protocol technique in the optimal therapeutic strategy of non-functioning pituitary adenomas. Eur J Endocrinol 2002;146:179–86.

[4] Greenman Y, Ouaknine G, Veshchev I, Reider-Groswasser II, Segev Y, Stern N. Postoperative surveillance of clinically nonfunctioning pituitary macroadenomas: markers of tumour quiescence and regrowth. Clin Endocrinol (Oxf) 2003;58:763–9.

[5] Ferrante E, Ferraroni M, Castrignanò T, Menicatti L, Anagni M, Reimondo G, et al. Non-functioning pituitary adenoma database: a useful resource to improve the clinical management of pituitary tumors. Eur J Endocrinol 2006;155:823–9.

[6] Dekkers OM, Pereira AM, Roelfsema F, Voormolen JHC, Neelis KJ, Schroijen MA, et al. Observation alone after transsphenoidal surgery for nonfunctioning pituitary macroadenoma. J Clin Endocrinol Metab 2006;91:1796–801.

[7] van den Bergh ACM, van den Berg G, Schoorl MA, Sluiter WJ, van der Vliet AM, Hoving EW, et al. Immediate postoperative radiotherapy in residual nonfunctioning pituitary adenoma: beneficial effect on local control without additional negative impact on pituitary function and life expectancy. Int J Radiat Oncol Biol Phys 2007;67:863–9.

[8] Losa M, Mortini P, Barzaghi R, Ribotto P, Terreni MR, Marzoli SB, et al. Early results of surgery in patients with nonfunctioning pituitary adenoma and analysis of the risk of tumor recurrence. J Neurosurg 2008;108:525–32.

[9] O'Sullivan EP, Woods C, Glynn N, Behan LA, Crowley R, O'Kelly P, et al. The natural history of surgically treated but radiotherapy-naïve nonfunctioning pituitary adenomas. Clin Endocrinol (Oxf) 2009;71:709–14.

[10] Brochier S, Galland F, Kujas M, Parker F, Gaillard S, Raftopoulos C, et al. Factors predicting relapse of nonfunctioning pituitary macroadenomas after neurosurgery: a study of 142 patients. Eur J Endocrinol 2010;163:193–200.

[11] Reddy R, Cudlip S, Byrne JV, Karavitaki N, Wass JAH. Can we ever stop imaging in surgically treated and radiotherapy-naive patients with non-functioning pituitary adenoma? Eur J Endocrinol 2011;165:739–44.

[12] Chen Y, Wang CD, Su ZP, Chen YX, Cai L, Zhuge QC, et al. Natural history of postoperative nonfunctioning pituitary adenomas: a systematic review and meta-analysis. Neuroendocrinology 2012;96:333–42.

[13] Murad MH, Fernández-Balsells MM, Barwise A, Gallegos-Orozco JF, Paul A, Lane MA, et al. Outcomes of surgical treatment for nonfunctioning pituitary adenomas: a systematic review and meta-analysis. Clin Endocrinol (Oxf) 2010;73:777–91.

[14] Roelfsema F, Biermasz NR, Pereira AM. Clinical factors involved in the recurrence of pituitary adenomas after surgical remission: a structured review and meta-analysis. Pituitary 2012;15:71–83.

[15] Pereira AM, Biermasz NR. Treatment of nonfunctioning pituitary adenomas: what were the contributions of the last 10 years? A critical view. Ann Endocrinol (Paris) 2012;73:111–6.

[16] Boelaert K, Gittoes NJ. Radiotherapy for non-functioning pituitary adenomas. Eur J Endocrinol 2001;144:569–75.

[17] Gittoes NJL. Radiotherapy for non-functioning pituitary tumors – when and under what circumstances? Pituitary 2003;6:103–8.

[18] Greenman Y, Stern N. Non-functioning pituitary adenomas. Best Pract Res Clin Endocrinol Metab 2009;23:625–38.

[19] Tanaka Y, Hongo K, Tada T, Sakai K, Kakizawa Y, Kobayashi S. Growth pattern and rate in residual nonfunctioning pituitary adenomas: correlations among tumor volume doubling time, patient age, and MIB-1 index. J Neurosurg 2003;98:359–65.

[20] Dubois S, Guyétant S, Menei P, Rodien P, Illouz F, Vielle B, et al. Relevance of Ki-67 and prognostic factors for recurrence/progression of gonadotropic adenomas after first surgery. Eur J Endocrinol 2007;157:141–7.

[21] Righi A, Agati P, Sisto A, Frank G, Faustini-Fustini M, Agati R, et al. A classification tree approach for pituitary adenomas. Hum Pathol 2012;43:1627–37.

[22] Yamada S, Ohyama K, Taguchi M, Takeshita A, Morita K, Takano K, et al. Study of the correlation between morphological findings and biological activities in clinically nonfunctioning pituitary adenomas. Neurosurgery 2007;61:580–4 [discussion 584–5].

[23] Bradley KJ, Wass JAH, Turner HE. Non-functioning pituitary adenomas with positive immunoreactivity for ACTH behave more aggressively than ACTH immunonegative tumours but do not recur more frequently. Clin Endocrinol (Oxf) 2003;58:59–64.

[24] Scheithauer BW, Jaap AJ, Horvath E, Kovacs K, Lloyd RV, Meyer FB, et al. Clinically silent corticotroph tumors of the pituitary gland. Neurosurgery 2000;47:723–9 [discussion 729–30].

[25] Webb KM, Laurent JJ, Okonkwo DO, Lopes MB, Vance ML, Laws Jr ER. Clinical characteristics of silent corticotrophic adenomas and creation of an internet-accessible database to facilitate their multi-institutional study. Neurosurgery 2003;53:1076–84 [discussion 1084–5].

[26] Cooper O, Ben-Shlomo A, Bonert V, Bannykh S, Mirocha J, Melmed S. Silent corticogonadotroph adenomas: clinical and cellular characteristics and long-term outcomes. Horm Cancer 2010;1:80–92.

[27] Trouillas J, Daniel L, Guigard M-P, Tong S, Gouvernet J, Jouanneau E, et al. Polysialylated neural cell adhesion molecules expressed in human pituitary tumors and related to extrasellar invasion. J Neurosurg 2003;98:1084–93.

[28] Mete O, Asa SL. Clinicopathological correlations in pituitary adenomas. Brain Pathol 2012;22:443–53.

[29] Trouillas J, Roy P, Sturm N, Dantony E, Cortet-Rudelli C, Viennet G, et al. A new prognostic clinicopathological classification of pituitary adenomas: a multicentric case-control study of 410 patients with 8 years post-operative follow-up. Acta Neuropathol 2013;126:123–35.

[30] Ramírez C, Cheng S, Vargas G, Asa SL, Ezzat S, González B, et al. Expression of Ki-67, PTTG1, FGFR4, and SSTR 2, 3, and 5 in nonfunctioning pituitary adenomas: a high throughput TMA, immunohistochemical study. J Clin Endocrinol Metab 2012;97:1745–51.

[31] Widhalm G, Wolfsberger S, Preusser M, Fischer I, Woehrer A, Wunderer J, et al. Residual nonfunctioning pituitary adenomas: prognostic value of MIB-1 labeling index for tumor progression. J Neurosurg 2009;111:563–71.

[32] Hsu C-Y, Guo W-Y, Chien C-P, Ho DM-T. MIB-1 labeling index correlated with magnetic resonance imaging detected tumor volume doubling time in pituitary adenoma. Eur J Endocrinol 2010;162:1027–33.

[33] Pisarek H, Kunert-Radek J, Radek M, Swietoslawski J, Winczyk K, Pawlikowski M. Expression of somatostatin receptor subtypes in primary and recurrent gonadotropinomas: are somatostatin receptors involved in pituitary adenoma recurrence? Neuro Endocrinol Lett 2011;32:96–101.

[34] Formosa R, Gruppetta M, Falzon S, Santillo G, DeGaetano J, Xuereb-Anastasi A, et al. Expression and clinical significance of Wnt players and survivin in pituitary tumours. Endocr Pathol 2012;23:123–31.

[35] Gazioglu NM, Erensoy N, Kadioglu P, Sayitoglu MA, Ersoy IH, Hatirnaz O, et al. Altered cyclin D1 genotype distribution in human sporadic pituitary adenomas. Med Sci Monit 2007;13:CR457–63.

[36] Onofri C, Theodoropoulou M, Losa M, Uhl E, Lange M, Arzt E, et al. Localization of vascular endothelial growth factor (VEGF) receptors in normal and adenomatous pituitaries: detection of a non-endothelial function of VEGF in pituitary tumours. J Endocrinol 2006;191:249–61.

[37] Cornelius A, Cortet-Rudelli C, Assaker R, Kerdraon O, Gevaert M-H, Prévot V, et al. Endothelial expression of endocan is strongly associated with tumor progression in pituitary adenoma. Brain Pathol 2012;22:757–64.

[38] Galland F, Lacroix L, Saulnier P, Dessen P, Meduri G, Bernier M, et al. Differential gene expression profiles of invasive and non-invasive non-functioning pituitary adenomas based on microarray analysis. Endocr Relat Cancer 2010;17:361–71.
[39] Wierinckx A, Raverot G, Nazaret N, Jouanneau E, Auger C, Lachuer J, et al. Proliferation markers of human pituitary tumors: contribution of a genome-wide transcriptome approach. Mol Cell Endocrinol 2010;326:30–9.
[40] Feng J, Hong L, Wu Y, Li C, Wan H, Li G, et al. Identification of a subtype-specific ENC1 gene related to invasiveness in human pituitary null cell adenoma and oncocytomas. J Neurooncol 2014;119:307–15.
[41] Hong L, Wu Y, Feng J, Yu S, Li C, Wu Y, et al. Overexpression of the cell adhesion molecule claudin-9 is associated with invasion in pituitary oncocytomas. Hum Pathol 2014;45:2423–9.
[42] Bonneville J-F, Cattin F, Bonneville F. Imaging of pituitary adenomas. Presse Med 2009;38:84–91.
[43] Kremer P, Forsting M, Ranaei G, Wüster C, Hamer J, Sartor K, et al. Magnetic resonance imaging after transsphenoidal surgery of clinically non-functional pituitary macroadenomas and its impact on detecting residual adenoma. Acta Neurochir (Vienna) 2002;144:433–43.
[44] Dekkers OM, Pereira AM, Romijn JA. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. J Clin Endocrinol Metab 2008;93:3717–26.
[45] Brada M, Rajan B, Traish D, Ashley S, Holmes-Sellors PJ, Nussey S, et al. The long-term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. Clin Endocrinol (Oxf) 1993;38:571–8.
[46] Jaffrain-Rea ML, Derome P, Bataini JP, Thomopoulos P, Bertagna X, Luton JP. Influence of radiotherapy on long-term relapse in clinically non-secreting pituitary adenomas. A retrospective study (1970–1988). Eur J Med 1993;2:398–403.
[47] Tsang RW, Brierley JD, Panzarella T, Gospodarowicz MK, Sutcliffe SB, Simpson WJ. Radiation therapy for pituitary adenoma: treatment outcome and prognostic factors. Int J Radiat Oncol Biol Phys 1994;30:557–65.
[48] Gittoes NJ, Bates AS, Tse W, Bullivant B, Sheppard MC, Clayton RN, et al. Radiotherapy for non-function pituitary tumours. Clin Endocrinol (Oxf) 1998;48:331–7.
[49] Park P, Chandler WF, Barkan AL, Orrego JJ, Cowan JA, Griffith KA, et al. The role of radiation therapy after surgical resection of nonfunctional pituitary macroadenomas. Neurosurgery 2004;55:100–6 [discussion 106–7].
[50] Olsson DS, Buchfelder M, Schlaffer S, Bengtsson B-A, Jakobsson K-E, Johannsson G, et al. Comparing progression of non-functioning pituitary adenomas in hypopituitarism patients with and without long-term GH replacement therapy. Eur J Endocrinol 2009;161:663–9.
[51] Breen P, Flickinger JC, Kondziolka D, Martinez AJ. Radiotherapy for nonfunctional pituitary adenoma: analysis of long-term tumor control. J Neurosurg 1998;89:933–8.
[52] Flickinger JC, Nelson PB, Martinez AJ, Deutsch M, Taylor F. Radiotherapy of nonfunctional adenomas of the pituitary gland. Results with long-term follow-up. Cancer 1989;63:2409–14.
[53] Milker-Zabel S, Debus J, Thilmann C, Schlegel W, Wannenmacher M. Fractionated stereotactically guided radiotherapy and radiosurgery in the treatment of functional and nonfunctional adenomas of the pituitary gland. Int J Radiat Oncol Biol Phys 2001;50:1279–86.
[54] Paek SH, Downes MB, Bednarz G, Keane WM, Werner-Wasik M, Curran Jr WJ, et al. Integration of surgery with fractionated stereotactic radiotherapy for treatment of nonfunctioning pituitary macroadenomas. Int J Radiat Oncol Biol Phys 2005;61:795–808.
[55] Colin P, Jovenin N, Delemer B, Caron J, Grulet H, Hecart A-C, et al. Treatment of pituitary adenomas by fractionated stereotactic radiotherapy: a prospective study of 110 patients. Int J Radiat Oncol Biol Phys 2005;62:333–41.
[56] Minniti G, Traish D, Ashley S, Gonsalves A, Brada M. Fractionated stereotactic conformal radiotherapy for secreting and nonsecreting pituitary adenomas. Clin Endocrinol (Oxf) 2006;64:542–8.
[57] Schalin-Jäntti C, Valanne L, Tenhunen M, Setälä K, Paetau A, Sane T, et al. Outcome of fractionated stereotactic radiotherapy in patients with pituitary adenomas resistant to conventional treatments: a 5.25-year follow-up study. Clin Endocrinol (Oxf) 2010;73:72–7.
[58] Wowra B, Stummer W. Efficacy of gamma knife radiosurgery for nonfunctioning pituitary adenomas: a quantitative follow-up with magnetic resonance imaging-based volumetric analysis. J Neurosurg 2002;97:429–32.
[59] Sheehan JP, Kondziolka D, Flickinger J, Lunsford LD. Radiosurgery for residual or recurrent nonfunctioning pituitary adenoma. J Neurosurg 2002;97:408–14.
[60] Petrovich Z, Yu C, Giannotta SL, Zee C-S, Apuzzo MLJ. Gamma knife radiosurgery for pituitary adenoma: early results. Neurosurgery 2003;53:51–9 [discussion 59–61].
[61] Iwai Y, Yamanaka K, Yoshioka K, Yoshimura M, Honda Y, Matsusaka Y, et al. The usefulness of adjuvant therapy using gamma knife radiosurgery for the recurrent or residual nonfunctioning pituitary adenomas. No Shinkei Geka 2005;33:777–83.
[62] Picozzi P, Losa M, Mortini P, Valle MA, Franzin A, Attuati L, et al. Radiosurgery and the prevention of regrowth of incompletely removed nonfunctioning pituitary adenomas. J Neurosurg 2005;102(Suppl.):71–4.
[63] Mingione V, Yen CP, Vance ML, Steiner M, Sheehan J, Laws ER, et al. Gamma surgery in the treatment of nonsecretory pituitary macroadenoma. J Neurosurg 2006;104:876–83.
[64] Liscák R, Vladyka V, Marek J, Simonová G, Vymazal J. Gamma knife radiosurgery for endocrine-inactive pituitary adenomas. Acta Neurochir (Vienna) 2007;149:999–1006 [discussion 1006].
[65] Pollock BE, Cochran J, Natt N, Brown PD, Erickson D, Link MJ, et al. Gamma knife radiosurgery for patients with nonfunctioning pituitary adenomas: results from a 15-year experience. Int J Radiat Oncol Biol Phys 2008;70:1325–9.
[66] Höybye C, Rähn T. Adjuvant gamma knife radiosurgery in non-functioning pituitary adenomas; low risk of long-term complications in selected patients. Pituitary 2009;12:211–6.
[67] Losa M, Picozzi P, Motta M, Valle M, Franzin A, Mortini P. The role of radiation therapy in the management of non-functioning pituitary adenomas. J Endocrinol Invest 2011;34:623–9.
[68] Wilson PJ, De-Loyde KJ, Williams JR, Smee RI. A single centre's experience of stereotactic radiosurgery and radiotherapy for non-functioning pituitary adenomas with the linear accelerator (LINAC). J Clin Neurosci 2012;19:370–4.
[69] Sheehan JP, Starke RM, Mathieu D, Young B, Sneed PK, Chiang VL, et al. Gamma knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study. J Neurosurg 2013;119:446–56.
[70] Lee C-C, Kano H, Yang H-C, Xu Z, Yen C-P, Chung W-Y, et al. Initial gamma knife radiosurgery for nonfunctioning pituitary adenomas. J Neurosurg 2014;120:647–54.
[71] Chen Y, Li ZF, Zhang FX, Li JX, Cai L, Zhuge QC, et al. Gamma knife surgery for patients with volumetric classification of nonfunctioning pituitary adenomas: a systematic review and meta-analysis. Eur J Endocrinol 2013;169:487–95.
[72] Iwata H, Sato K, Tatewaki K, Yokota N, Inoue M, Baba Y, et al. Hypofractionated stereotactic radiotherapy with CyberKnife for nonfunctioning pituitary adenoma: high local control with low toxicity. Neuro Oncol 2011;13:916–22.
[73] Erridge SC, Conkey DS, Stockton D, Strachan MWJ, Statham PFX, Whittle IR, et al. Radiotherapy for pituitary adenomas: long-term efficacy and toxicity. Radiother Oncol 2009;93:597–601.
[74] Minniti G, Traish D, Ashley S, Gonsalves A, Brada M. Risk of second brain tumor after conservative surgery and radiotherapy for pituitary adenoma: update after an additional 10 years. J Clin Endocrinol Metab 2005;90:800–4.
[75] Berkmann S, Tolnay M, Hänggi D, Ghaffari A, Gratzl O. Sarcoma of the sella after radiotherapy for pituitary adenoma. Acta Neurochir (Vienna) 2010;152:1725–35.
[76] Tooze A, Gittoes NJ, Jones CA, Toogood AA. Neurocognitive consequences of surgery and radiotherapy for tumours of the pituitary. Clin Endocrinol (Oxf) 2009;70:503–11.
[77] van Beek AP, van den Bergh ACM, van den Berg LM, van den Berg G, Keers JC, Langendijk JA, et al. Radiotherapy is not associated

with reduced quality of life and cognitive function in patients treated for nonfunctioning pituitary adenoma. Int J Radiat Oncol Biol Phys 2007;68:986–91.
[78] Schultz-Hector S, Trott K-R. Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with the radiobiologic data? Int J Radiat Oncol Biol Phys 2007;67:10–8.
[79] Ayuk J. Does pituitary radiotherapy increase the risk of stroke and, if so, what preventative actions should be taken? Clin Endocrinol (Oxf) 2012;76:328–31.
[80] Stewart FA, Heeneman S, Te Poele J, Kruse J, Russell NS, Gijbels M, et al. Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE-/- mice and predisposes to an inflammatory plaque phenotype prone to hemorrhage. Am J Pathol 2006;168:649–58.
[81] Brada M, Burchell L, Ashley S, Traish D. The incidence of cerebrovascular accidents in patients with pituitary adenoma. Int J Radiat Oncol Biol Phys 1999;45:693–8.
[82] Rim CH, Yang DS, Park YJ, Yoon WS, Lee JA, Kim CY. Radiotherapy for pituitary adenomas: long-term outcome and complications. Radiat Oncol J 2011;29:156–63.
[83] Chand-Fouché M-E, Colin P, Bondiau P-Y. Pituitary adenomas: multimodal management and modern irradiation techniques. Cancer Radiother 2012;16(Suppl.):S90–100.
[84] Cifarelli CP, Schlesinger DJ, Sheehan JP. Cranial nerve dysfunction following gamma knife surgery for pituitary adenomas: long-term incidence and risk factors. J Neurosurg 2012;116:1304–10.
[85] Stafford SL, Pollock BE, Leavitt JA, Foote RL, Brown PD, Link MJ, et al. A study on the radiation tolerance of the optic nerves and chiasm after stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 2003;55:1177–81.
[86] Pollock BE, Link MJ, Leavitt JA, Stafford SL. Dose-volume analysis of radiation-induced optic neuropathy after single-fraction stereotactic radiosurgery. Neurosurgery 2014;75:456–60 [discussion 460].
[87] Tishler RB, Loeffler JS, Lunsford LD, Duma C, Alexander 3rd E, Kooy HM, et al. Tolerance of cranial nerves of the cavernous sinus to radiosurgery. Int J Radiat Oncol Biol Phys 1993;27:215–21.
[88] Kuo JS, Chen JCT, Yu C, Zelman V, Giannotta SL, Petrovich Z, et al. Gamma knife radiosurgery for benign cavernous sinus tumors: quantitative analysis of treatment outcomes. Neurosurgery 2004;54:1385–93 [discussion 1393–4].
[89] Liu A-L, Wang C, Sun S, Wang M, Liu P. Gamma knife radiosurgery for tumors involving the cavernous sinus. Stereotact Funct Neurosurg 2005;83:45–51.
[90] Much JW, Weber ED, Newman SA. Ocular neuromyotonia after gamma knife stereotactic radiation therapy. J Neuroophthalmol 2009;29:136–9.
[91] Feigl GC, Bonelli CM, Berghold A, Mokry M. Effects of gamma knife radiosurgery of pituitary adenomas on pituitary function. J Neurosurg 2002;97:415–21.
[92] Leenstra JL, Tanaka S, Kline RW, Brown PD, Link MJ, Nippoldt TB, et al. Factors associated with endocrine deficits after stereotactic radiosurgery of pituitary adenomas. Neurosurgery 2010;67:27–32 [discussion 32–3].
[93] Marek J, Jezková J, Hána V, Krsek M, Bandúrová L, Pecen L, et al. Is it possible to avoid hypopituitarism after irradiation of pituitary adenomas by the Leksell gamma knife? Eur J Endocrinol 2011;164:169–78.
[94] Lim YJ, Leem W, Park JT, Kim TS, Rhee BA, Kim GK. Cerebral infarction with ICA occlusion after gamma knife radiosurgery for pituitary adenoma: a case report. Stereotact Funct Neurosurg 1999;72(Suppl. 1):132–9.
[95] Loeffler JS, Niemierko A, Chapman PH. Second tumors after radiosurgery: tip of the iceberg or a bump in the road? Neurosurgery 2003;52:1436–40 [discussion 1440–2].
[96] Sasagawa Y, Tachibana O, Iizuka H. Undifferentiated sarcoma of the cavernous sinus after γ knife radiosurgery for pituitary adenoma. J Clin Neurosci 2013;20:1152–4.
[97] Killory BD, Kresl JJ, Wait SD, Ponce FA, Porter R, White WL. Hypofractionated CyberKnife radiosurgery for perichiasmatic pituitary adenomas: early results. Neurosurgery 2009;64:A19–25.
[98] Pivonello R, Matrone C, Filippella M, Cavallo LM, Di Somma C, Cappabianca P, et al. Dopamine receptor expression and function in clinically nonfunctioning pituitary tumors: comparison with the effectiveness of cabergoline treatment. J Clin Endocrinol Metab 2004;89:1674–83.
[99] Gabalec F, Beranek M, Netuka D, Masopust V, Nahlovsky J, Cesak T, et al. Dopamine 2 receptor expression in various pathological types of clinically non-functioning pituitary adenomas. Pituitary 2012;15:222–6.
[100] Neto LV, Wildemberg LE, Moraes AB, Colli LM, Kasuki L, Marques NV, et al. Dopamine receptor subtype 2 expression profile in non-functioning pituitary adenomas and in vivo response to cabergoline therapy. Clin Endocrinol (Oxf) 2014.
[101] Taboada GF, Luque RM, Bastos W, Guimarães RFC, Marcondes JB, Chimelli LMC, et al. Quantitative analysis of somatostatin receptor subtype (SSTR1-5) gene expression levels in somatotropinomas and nonfunctioning pituitary adenomas. Eur J Endocrinol 2007;156:65–74.
[102] Greenman Y, Tordjman K, Osher E, Veshchev I, Shenkerman G, Reider-Groswasser II, et al. Postoperative treatment of clinically nonfunctioning pituitary adenomas with dopamine agonists decreases tumour remnant growth. Clin Endocrinol (Oxf) 2005;63:39–44.
[103] Colao A, Di Somma C, Pivonello R, Faggiano A, Lombardi G, Savastano S. Medical therapy for clinically non-functioning pituitary adenomas. Endocr Relat Cancer 2008;15:905–15.
[104] Plöckinger U, Reichel M, Fett U, Saeger W, Quabbe HJ. Preoperative octreotide treatment of growth hormone-secreting and clinically nonfunctioning pituitary macroadenomas: effect on tumor volume and lack of correlation with immunohistochemistry and somatostatin receptor scintigraphy. J Clin Endocrinol Metab 1994;79:1416–23.
[105] Broson-Chazot F, Houzard C, Ajzenberg C, Nocaudie M, Duet M, Mundler O, et al. Somatostatin receptor imaging in somatotroph and nonfunctioning pituitary adenomas: correlation with hormonal and visual responses to octreotide. Clin Endocrinol (Oxf) 1997;47:589–98.
[106] Andersen M, Bjerre P, Schrøder HD, Edal A, Høilund-Carlsen PF, Pedersen PH, et al. In vivo secretory potential and the effect of combination therapy with octreotide and cabergoline in patients with clinically nonfunctioning pituitary adenomas. Clin Endocrinol (Oxf) 2001;54:23–30.
[107] Zatelli MC, Piccin D, Vignali C, Tagliati F, Ambrosio MR, Bondanelli M, et al. Pasireotide, a multiple somatostatin receptor subtypes ligand, reduces cell viability in non-functioning pituitary adenomas by inhibiting vascular endothelial growth factor secretion. Endocr Relat Cancer 2007;14:91–102.
[108] Dworakowska D, Wlodek E, Leontiou CA, Igreja S, Cakir M, Teng M, et al. Activation of RAF/MEK/ERK and PI3K/AKT/mTOR pathways in pituitary adenomas and their effects on downstream effectors. Endocr Relat Cancer 2009;16:1329–38.
[109] Cerovac V, Monteserin-Garcia J, Rubinfeld H, Buchfelder M, Losa M, Florio T, et al. The somatostatin analogue octreotide confers sensitivity to rapamycin treatment on pituitary tumor cells. Cancer Res 2010;70:666–74.